

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

|                  |                                                                     |                   |             |
|------------------|---------------------------------------------------------------------|-------------------|-------------|
| Applicant:       | Khalid K. Sadozai et al.                                            | Confirmation No.: | 5063        |
| Application No.: | 10/743,557                                                          | Art Unit:         | 1616        |
| Filed:           | December 22, 2003                                                   | Examiner:         | C. A. Brown |
| Title:           | CROSSLINKED HYALURONIC ACID COMPOSITIONS FOR<br>TISSUE AUGMENTATION |                   |             |

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**APPEAL BRIEF**

Dear Sir:

As required under § 41.37(a), this brief is filed after the Notice of Appeal filed in this case on February 7, 2011, and is in furtherance of said Notice of Appeal.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

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**I. REAL PARTY IN INTEREST**

The real party in interest for this appeal is:

Anika Therapeutics, Inc., 32 Wiggins Avenue, Bedford, MA 01730.

**II. RELATED APPEALS AND INTERFERENCES**

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

**III. STATUS OF CLAIMS**

**A. Total Number of Claims in Application**

There are 12 claims pending in application.

**B. Current Status of Claims**

1. Claims canceled: 1-10 and 23-48
2. Claims withdrawn from consideration but not canceled: None
3. Claims pending: 11-22
4. Claims allowed: None
5. Claims rejected: 11-22

**C. Claims On Appeal**

The claims on appeal are claims 11-22.

#### IV. STATUS OF AMENDMENTS

All amendments that have been submitted have been accepted and Appendix A presents the pending claims including all amendments that have been accepted.

#### V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention provides a method for tissue augmentation, e.g., a method of injecting a dermal tissue-filling composition into a patient. A composition suitable for tissue augmentation needs to be able to fill the space in the tissue of the patient. It cannot contain too much water because, over time, water evaporates or gets absorbed, thus reducing the volume of the tissue-filling composition. Moreover, the composition cannot be metabolized rapidly by the tissue, as this would again reduce the volume of the composition. On the other hand, the composition needs to be suitable for administration by injection, i.e., it cannot be solid or too viscous. The challenge in making an effective composition for tissue augmentation is to balance its mechanical and biostability properties with its suitability for administration by injection through a fine needle.

Accordingly, the invention relates to a method of augmenting tissue in a subject that is in need of tissue augmentation. The method includes the step of inserting a needle into a subject at a location in the subject that is in need of tissue augmentation, wherein the needle is coupled to a syringe loaded with a hyaluronic acid ("HA") composition. The method further includes applying force to the syringe, whereby at least a portion of the HA composition is delivered into the subject. (See pg. 3, lines 15-19). The HA composition has specific properties tailored to tissue augmentation by way of an injection.

The HA composition includes crosslinked, water-insoluble, hydrated HA gel particles. For example, any liquid in the composition is essentially contained in the hydrated particles, i.e., there is essentially no free liquid phase. (See pg. 12, lines 5-9). The HA includes crosslinks represented by the following structural formula:



Each HA' is the same or different crosslinked HA' molecule, i.e., the crosslinks can be intramolecular or intermolecular. Each U is independently an optionally substituted O-acyl isourea or N-acyl urea. R<sub>2</sub> is optionally substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl aryl, heteroaryl, heterocyclyl, cycloaliphaticalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl. (See pg. 3, lines 5-14).

The HA gel particles have an average particle diameter distribution selected from the group consisting of a hydrated particle average diameter between about 20 µm and about 1000 µm, and a dehydrated particle average diameter between about 10 µm and about 500 µm. (See pg. 11, lines 24-28). Advantages of the recited particle size for use in the claimed method of tissue augmentation are that they flow well, fill the tissue defects well, and are injectable through a fine gauge needle.

The crosslinked HA composition is a single hydrated particle phase, e.g., any liquid in the composition is essentially contained in the hydrated particles, e.g., there is essentially no free liquid phase. (see pg. 12, lines 5-9). Therefore, as the water does not evaporate from the composition, there is no need for frequent injections and the tissue augmenting effect is present for a long time.

The crosslinked HA composition is stable in the subject for at least 8 weeks. (See pg. 30, line 12 – pg. 31, line 6). This property eliminates the need for frequent injections and therefore improves patient compliance.

Claim 11 is presented in the following table which maps the recited elements to the relevant portions of the specification:

| Features of Claim                                                                                             | Support in Specification |
|---------------------------------------------------------------------------------------------------------------|--------------------------|
| 11. A method of augmenting tissue in a subject that is in need of tissue augmentation, the method comprising: | pg. 3, lines 15-18       |
| a) inserting a needle into a subject at a location in the subject that is in need of tissue                   | pg. 3, lines 15-18       |

| Features of Claim                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Support in Specification   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| <p>augmentation, wherein the needle is coupled to a syringe loaded with a crosslinked HA composition that includes crosslinked, water-insoluble, hydrated HA gel particles,</p>                                                                                                                                                                                                                                                                                                                                                                      | <p>pg. 3, lines 5-6</p>    |
| <p>wherein the HA includes crosslinks represented by the following structural formula:</p> $\text{HA}'-\text{U}-\text{R}_2-\text{U}-\text{HA}'$ <p>wherein:</p> <p>each HA' is the same or different crosslinked HA' molecule;</p> <p>each U is independently an optionally substituted O-acyl isourea or N-acyl urea;</p> <p>and R<sub>2</sub> is optionally substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl aryl, heteroaryl, heterocycl, cycloaliphaticalkyl, aralkyl, heteroaralkyl, or heterocyclalkyl,</p> | <p>pg. 3, lines 5-14</p>   |
| <p>wherein the HA gel particles have an average particle diameter distribution selected from the group consisting of a</p>                                                                                                                                                                                                                                                                                                                                                                                                                           | <p>pg. 11, lines 24-28</p> |

| Features of Claim                                                                                                                                                                                        | Support in Specification         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| hydrated particle average diameter between about 20 $\mu\text{m}$ and about 1000 $\mu\text{m}$ , and a dehydrated particle average diameter between about 10 $\mu\text{m}$ and about 500 $\mu\text{m}$ ; |                                  |
| wherein the crosslinked HA composition is a single hydrated particle phase; and                                                                                                                          | pg. 12, lines 5-9                |
| b) applying force to the syringe, whereby at least a portion of the crosslinked HA composition is delivered into the subject;                                                                            | pg. 3, lines 18-19               |
| wherein the crosslinked HA composition is stable in the subject for at least 8 weeks.                                                                                                                    | pg. 30, line 12 – pg. 31, line 6 |

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Examiner rejected claims 11-22 under 35. U.S.C. § 103(a) as allegedly being unpatentable over (1) U.S. Pat. No. 5,143,724 to Leshchiner et al. (“Leshchiner”) in combination with (2) JP 2000230001 to Fujita et al. (“Fujita”) in view of (3) U.S. Pat. No. 5,942,241 to Chasin et al. (“Chasin”), (4) U.S. Pat. No. 7,196,180 to Aeschlimann et al. (“Aeschlimann”), and (5) U.S. Pat. No. 6,521,223 to Calias et al. (“Calias”). Claims 11-22 stand and fall together.

## VII. ARGUMENT

The Examiner appears to have decided to search for each limitation found in the claims separately and then combine such references to set up an obviousness rejection. Therefore, it is not surprising that in the instant § 103 rejection the Examiner cites five (5) unrelated references.

An obviousness rejection is not sustainable when the record lacks substantial evidence showing all the limitations in the claims. *In re McNeil-PPC, Inc.*, 574 F.3d 1393,1400,91 U.S.P.Q.2d 1576, 1581 (Fed. Cir. 2009) (reversing the rejection, because "[t]here is not substantial evidence, indeed, no evidence, that Sasaki discloses ribs 'compressed less than the fiber core' or 'a generally cylindrical compressed, solid fiber core'"). As in *McNeil* and as required by MPEP § 2143 (A), (B), and (E), the Examiner has not shown that all of the recited limitations in the claims of instant Claim 11 were shown or suggested in the prior art. Accordingly, the rejection is not sustainable and should be withdrawn.

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art, is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). “When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious.” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. at 416, 82 USPQ2d at 1395.

**A. Claim 11**

For at least the reasons presented below, we submit that combining the teaching of Leshchiner with the teachings of Fujita, Chasin, Aeschlimann, and Calias, does not teach or suggest the invention of Claim 11.

**1. Cited references do not teach the crosslinked HA composition of Claim 11**

Claim 11 recites, *inter alia*, that “HA includes crosslinks represented by the following structural formula:  $HA'-U-R_2-U-HA'$  wherein: each HA' is the same or different crosslinked HA' molecule; each U is independently an optionally substituted O-acyl isourea or N-acyl urea; and R<sub>2</sub> is optionally substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl aryl, heteroaryl, heterocyclyl, cycloaliphaticalkyl, aralkyl, heteroaralkyl, or heterocyclalkyl.” (Claim 11, emphasis added).

We note that crosslinked HA having the structural formula:  $HA'-U-R_2-U-HA'$ , as recited in Claim 11, is not taught in any of the cited references.

The Examiner argued that this limitation is taught in Aeschlimann, relying on the teachings of col. 12, line 48 – col. 13, line 5. (Office Action, pg. 8, ¶2). We note, however, that the Examiner’s characterization of Aeschlimann is not accurate. Aeschlimann teaches methods of making derivatized HA that do not result in the crosslinked HA recited in Claim 11.



Aeschlimann is directed to “a method for more versatile modification of HA with various functional groups that allow for crosslinking of the HA derivatives under physiological conditions.” (col. 4, lines 52-54, emphasis added). In other words, Aeschlimann is concerned with methods for making HA with functionalized groups that can then be used for production of crosslinked HA, not with methods of making crosslinked HA derivatives.

This is evident, e.g., from reaction (IV) in col. 13 of Aeschlimann. The reaction product is HA-CO-NH-R, which is an amide (as it has the amide (-CO-NH-) bond), which is a functionalized HA, not a crosslinked HA. The crosslinked HA recited in Claim 11, has two HA molecules linked together (hence it is referred to as being “crosslinked”) and is of the form HA'-U-R<sub>2</sub>-U-HA', where U is independently an optionally substituted O-acyl isourea or N-acyl urea and each HA' is the same or different HA molecule (meaning the crosslink can be intermolecular or intramolecular). The structure of crosslinked HA in instant Claim 11 is explained in the application at pg. 9, line 27 – pg. 10, line 9, as well as in the definition of HA'-U-R<sub>2</sub>-U-HA' provided in Claim 11. Similar analysis can be applied to reaction (VI) in col. 13 of Aeschlimann, which also results in a final product that is a functionalized HA and is outside the scope of the crosslinked HA recited in Claim 11.

Not surprisingly, the section of Aeschlimann cited by the Examiner (Office Action, pg. 8, ¶2), describes the use of functionalizing agent EDC (i.e., 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide), which -- when reacted with HA -- provides an HA having a reactive group. Significantly, reaction of HA with EDC does not produce crosslinked HA. This is because EDC has only one reactive group for coupling to HA and, therefore, cannot be used to form crosslinked HA, much less crosslinked HA having the structural formula HA'—U—R<sub>2</sub>—U—HA' recited in Claim 11. As discussed in the instant application, crosslinked HA having the structural formula HA'—U—R<sub>2</sub>—U—HA' can be generated using biscarbodiimides (e.g., pg. 8, lines 9-13). Aeschlimann, however, does not contemplate the use of biscarbodiimides to crosslink HA.

Leshchiner, Fujita, Chasin, and Calias do not remedy the deficiencies of Aeschlimann, at least because they do not teach or suggest the crosslinked HA composition recited in Claim 11.

Accordingly, the combination of cited references does not teach or suggest the crosslinked HA of Claim 11, and the Examiner's rejection should be reversed.

**2. Cited references do not teach a crosslinked HA composition that is "a single hydrated particle phase"**

As explained below, the five cited references, alone or in combination, do not disclose the claim element "wherein the crosslinked HA composition is a single hydrated particle phase." The Application teaches that "a single hydrated particle phase" means that "any liquid in the composition is essentially contained in the hydrated particles, e.g., there is essentially no free liquid phase." (See pg. 12, lines 5-9).

The Examiner has conceded that the single hydrated particle phase is not taught or suggested by the combination of Lehschiner, Fujita, Chasin and Aeschlimann. (Office Action mailed January 25, 2010, pg. 2). However, the Examiner now contends that this limitation is taught by Calias. We note, however, that the Examiner's characterization of the teachings of Calias is not accurate.

Preliminarily, Appellants note that Calias is directed to single-phase gels for prevention of surgical adhesions and the method of their preparation, i.e., a purpose different than the method of Claim 11.

First, Calias teaches compositions in which a solid is precipitated from solution (Abstract). Because such compositions contain a solution/solvent (a liquid phase) and a precipitated solid (a solid phase), these are two-phase compositions which do not meet the "single hydrated particle phase" element of Claim 11. The purpose of precipitating the gel in Calias is not to create a "single hydrated particle phase," but to store it until it is desirable to reconstitute it by rehydrating the powder. (col. 3, lines 38-41, emphasis added). Therefore, the precipitated solid in Calias is a dehydrated powder (as it needs to be rehydrated), not a hydrated particle (or a hydrated particle phase) recited in Claim 11.

Second, Calias teaches that the solid precipitated from the solution “can be redissolved in water to form a gel.” (Abstract). A gel is not “a single hydrated particle phase” as recited in Claim 11 and discussed above.

Third, Claim 11 recites that the gel particles are “water-insoluble.” To the extent that Calias teaches that its gels are “water-insoluble” (col. 4, lines 19-21), Calias defines a “water-insoluble” gel as “a gel, which when prepared under conditions as described for a water soluble gel, is structurally intact after 20 minutes.” (col. 5, lines 62-65). Accordingly, Calias is directed to the preparation of soluble gels, which are then classified as “insoluble” if they remain structurally intact in water for 20 minutes. Such gels, however, are not suitable for the method of tissue augmentation recited in Claim 11, where longer-term stability, such as for at least 8 weeks, is important. Accordingly, the instant specification defines the term “water-insoluble” to mean that “upon placing the particles of the HA composition in water at neutral pH and 25°C for at least about 2 weeks [or more], the HA in the particles is essentially undissolved, e.g., essentially no HA from the particles becomes freely dissolved in the water.” (pg. 11, lines 3-12, emphasis added). Thus, the gels that Calias would call “water-insoluble” (i.e., if they are stable for 20 minutes) would most likely not be considered water-insoluble according to the test provided in the instant application, which requires that the HA particles remain essentially undissolved in water for at least about 2 weeks. Claim 11, however, requires that the HA composition is stable in the subject for at least 8 weeks.

Fourth, Calias is directed to compositions for preventing the formation of surgical adhesions. As Calias explains, such compositions need to be, *inter alia*, bioabsorbable (col. 1, lines 33-44). Consequently, the gels of Calias are described as being “bioabsorbable.” (col. 4, lines 17-19). Calias defines “bioabsorbable” as a substance “which is maintained in the body in a relatively intact form for at least about 7 days, and is then completely absorbed by the body after about 30 days thereafter.” (col. 5, lines 30-33, emphasis added). These properties are incompatible with the claimed properties of the composition recited in Claim 11. Claim 11 relates to a method of tissue augmentation in which the composition is stable in the subject for at least 8 weeks.

Fifth, modifying the composition of Calias to be suitable in the invention of Claim 11 would require making it unsuitable for its purposes, as the requirement that the composition be stable in the subject for at least 8 weeks (56 days) would make it unsuitable for the purpose described in Calias, which requires that the composition is completely absorbed by the body after about 30 days.

Leshchiner, Fujita, Chasin, and Aeschlimann do not remedy the deficiencies of Calias, at least because they do not teach or suggest a crosslinked HA composition that is “a single hydrated particle phase,” as recited in Claim 11.

Accordingly, the combination of cited references does not teach or suggest the crosslinked HA composition that is “a single hydrated particle phase” as recited in Claim 11, and the Examiner’s rejection should be reversed.

### **3. Cited references teach away from the invention of Claim 11**

The Examiner has not argued that the “wherein the crosslinked HA composition is stable in the subject for at least 8 weeks” claim element is taught or suggested by the combination of cited references. To supplement the missing claim element, the Examiner stated that because “the prior art contains the exact same ingredients...” the burden is shifted on the Applicant (Appellant) to prove that the cited references do not contain this property.

As explained above, the cited references do not contain the exact same ingredients, at least because they do not teach: (1) the crosslinked composition recited in Claim 11; and (2) a composition wherein “the crosslinked HA composition is a single hydrated particle phase” as recited in Claim 11. Accordingly, the burden has not been shifted to the Appellants.

Importantly, because Calias teaches that its compositions are completely absorbed by the body after 30 days (or 37 days, depending on the interpretation of what “thereafter” refers to) (*see* col. 5, lines 30-33), the combination of cited references actually teaches away from the invention of Claim 11, which requires that the composition is “stable in the subject for at least 8 weeks,” i.e., at least 56 days.

Therefore, the Examiner's rejection should be reversed.

**4. The Examiner's has not established a reason to combine the five (5) cited references**

Notably, the Examiner did not even attempt to provide any reasoning for combining the five (5) cited references, but instead only attempted to reason why *three* different *subgroups* of these five (5) references are combinable. Appellants are not aware of any authority that allows the Examiner to do this. Accordingly, the Examiner's rejection should be reversed.

Nevertheless, Appellants will address the Examiner's arguments below.

*A. Fujita and Chasin do not teach a method of tissue augmentation and contradict Examiner's reasoning for their combination with Leshchiner*

The Examiner states that each of Fujita, Leshchiner and Chasin "teach hyaluronic acid compositions useful in a method of augmenting tissue." (Office Action mailed August 5, 2010, pg. 9, last ¶). This is not accurate.

Fujita teaches a gel slurry (i.e., a two-phase composition) that is suitable for *in vivo decomposable medical materials*, including cosmetics (Abstract, emphasis added). Use in cosmetics is not equal to a method of tissue augmentation. Moreover, the Examiner conceded that the gel slurry of Fujita is not a single hydrated particle phase (Office Action mailed January 25, 2010, pg. 8, ¶2).

As the title and abstract of Chasin indicate, Chasin is concerned with formulations and methods for providing *controlled local anesthesia*. A method for providing controlled local anesthesia is clearly not a method for tissue augmentation as described and presently claimed in the instant application.

Chasin teaches that the applications of its compositions "include any condition for which localized nerve blockade is desirable. This includes both *local anesthesia* for the relief of pain and

motor symptoms as well as local anesthesia for other medical purposes.” (Col. 18, lines 58-63, emphasis added). Moreover, Chasin describes that the “[a]ugmenting agents according to the invention are compositions or compounds that prolong the duration of local anesthesia and/or enhance the effectiveness of local anesthetic agents when delivered to the site of local anesthetic administration before, simultaneously with or after the local anesthetic is administered.” (Col. 6, lines 57-64, emphasis added). Thus, the term “augmenting agent” in Chasin relates to an agent having an anesthetic effect, not a tissue enhancing effect as contemplated in the present application. Further examples of “augmenting agents” in Chasin are discussed in Col. 6, line 66 – Col. 9, line 25. Hyaluronic acid or its derivatives are not mentioned as examples of augmenting agents in Chasin, but are only mentioned as excipients or carriers for a local anesthetic or the augmenting agent (Col. 12, lines 26-56; Col. 14, lines 1-7, emphasis added).

Therefore, the Examiner’s reasoning that these references should be combined because they teach compositions used for the same purpose (Office Action mailed August 5, 2010, pg. 10, ¶1) is incorrect, and is contradicted by the teachings of Fujita and Chasin.

Accordingly, the Examiner’s reasoning that “claims that require no more than mixing together two or three conventional hyaluronic acid compositions” are *prima facie* obvious (Id.) does not stand to reason, as mixing the compositions disclosed in these references clearly does not result in the composition recited in Claim 11.

Therefore, the Examiner’s rejection should be reversed.

*B. The Examiner erred in combining Fujita, Leshchiner and Aeschliman*

As discussed above, Fujita does not teach a method of tissue augmentation. Therefore, the Examiner’s reasoning that these references should be combined because they teach compositions used for the same purpose (Office Action mailed August 5, 2010, pg. 10, ¶2) is incorrect, and is contradicted by the teachings of Fujita.

Finally, as Appellants have argued during the prosecution of this application, the combination of Fujita, Leshchiner and Aeschliman does not teach all the limitations of Claim 11. For example, this combination of references does not teach (1) the crosslinks of the type recited in Claim 11; and (2) a composition wherein “the crosslinked HA composition is a single hydrated particle phase” as recited in Claim 11.

Nor do these references teach how the claimed crosslinked HA composition could be made. Accordingly, the Examiner’s reasoning that “claims that require no more than mixing together two or three conventional hyaluronic acid compositions” are *prima facie* obvious (Id.) does not stand to reason, as mixing the compositions disclosed in these references clearly does not result in the composition recited in Claim 11. Therefore, the Examiner’s rejection should be reversed.

*C. The Examiner erred in combining Fujita, Leshchiner and Calias*

As discussed above, Fujita does not teach a method of tissue augmentation. As also discussed above, Calias also does not teach a method of tissue augmentation, but instead is directed to single-phase gels for prevention of surgical adhesions and the method of their preparation.

Finally, as Appellants have argued during the prosecution of this application, the combination of Fujita, Leshchiner and Calias does not teach all the limitations of Claim 11. For example, this combination of references does not teach (1) the crosslinks of the type recited in Claim 11; and (2) a composition wherein “the crosslinked HA composition is a single hydrated particle phase” as recited in Claim 11.

Accordingly, the Examiner’s reasoning that “the prior art appears to contain the exact same ingredients” is incorrect and the burden has not been properly shifted to the Appellants. Therefore, the Examiner’s rejection should be reversed.

*D. The method of Claim 11 is not an identifiable, predictable solution*

In deciding nonobviousness, “[e]ach case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known

choices, the specificity or generality of the prior art, and the predictability of results in the area of interest." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008). When "an art is unpredictable, as the chemical arts often are, [a] focus on ... 'identified, predictable solutions' may present a difficult hurdle because predictable solutions are less likely to be genuinely predictable." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

The Examiner, misinterpreting Calias, has not shown that making a composition for tissue augmentation according to Claim 11 that is a single hydrated particle phase is an identifiable, much less a predictable solution.

*E. There is no reasonable expectation of success*

The Examiner appears to rely on the teachings of Calias to allege that a reasonable expectation of success to combine the teachings of the cited references "given the state of the art as evidenced by the teachings of the cited references." (Office Action mailed August 5, 2010, pg. 11). That does not stand to reason.

As discussed above, none of the cited references teach or suggest a composition that (1) is a single hydrated particle phase; and (2) has the crosslinks of the type required in Claim 11. Importantly, these references do not suggest why a person of skill in the art should make the claimed composition and use it in the claimed method, much less how one would make such composition. As discussed above, Calias even teaches away from the claimed invention. Therefore, the Examiner has not established that a reasonable expectation of success exists.

**5. Conclusion**

For the reasons presented above, we submit that the claims are in condition for allowance and therefore respectfully ask that they be allowed to issue.



## VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

This submission is accompanied by the payment of the fee required under § 41.20(b)(2) for filing this brief and the fee for a Petition for a Five-Month Extension of Time. Appellants believe no other fees are due with this submission. However, if an additional fee is due or to credit any overpayment, please charge or credit our Deposit Account No. 08-0219, under Order No. 0103343.00128US1 from which the undersigned is authorized to draw.

Respectfully submitted,

Dated: September 7, 2011

/Andrej Barbic/  
Andrej Barbic, Ph.D.  
Registration No.: 61,908  
Attorney for Applicant(s)

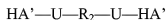
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**CLAIMS - APPENDIX A****Claims Involved in the Appeal of Application Serial No. 10/743,557:**

1-10. (Canceled)

11. (Previously Presented) A method of augmenting tissue in a subject that is in need of tissue augmentation, the method comprising:

a) inserting a needle into a subject at a location in the subject that is in need of tissue augmentation, wherein the needle is coupled to a syringe loaded with a crosslinked HA composition that includes crosslinked, water-insoluble, hydrated HA gel particles, wherein the HA includes crosslinks represented by the following structural formula:



wherein:

each HA' is the same or different crosslinked HA' molecule;

each U is independently an optionally substituted O-acyl isourea or N-acyl urea;

and R<sub>2</sub> is optionally substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl aryl, heteroaryl, heterocyclyl, cycloaliphaticalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl,

wherein the HA gel particles have an average particle diameter distribution selected from the group consisting of a hydrated particle average diameter between about 20 μm and about 1000 μm, and a dehydrated particle average diameter between about 10 μm and about 500 μm;

wherein the crosslinked HA composition is a single hydrated particle phase; and

b) applying force to the syringe, whereby at least a portion of the crosslinked HA composition is delivered into the subject;

wherein the crosslinked HA composition is stable in the subject for at least 8 weeks.

12. (Original) The method of claim 11, wherein the subject is human.
13. (Original) The method of claim 12, wherein the particles include at least one bioactive agent selected from the group consisting of cells, genes, proteins, antibodies, peptides, and pharmaceuticals.
14. (Previously Presented) The method of claim 13, wherein the bioactive agent includes an anesthetic.
15. (Previously Presented) The method of claim 14, wherein the anesthetic is lidocaine, mepivacaine, prilocaine, bupivacaine, cocaine, procaine, chlorocaine, or tetracaine, or a salt or solvate thereof.
16. (Previously Presented) The method of claim 15, wherein the anesthetic is lidocaine.HCl.
17. (Canceled)
18. (Previously Presented) The method of claim 12, wherein the distribution is a multimodal distribution.
19. (Original) The method of claim 18, wherein the HA in the composition consists essentially of the crosslinked, water-insoluble, hydrated HA gel particles.
20. (Previously Presented) The method of claim 12 wherein the crosslinked HA composition has at least one parameter measured at 37°C selected from a storage modulus  $G'$  of at least about 50 Pa when measured at 1 Hz frequency using a 4 cm flat geometry, and a kinematic viscosity of at least about 20,000 cPs when measured at a shear rate of  $1 \text{ s}^{-1}$ .

21. (Original) The method of claim 20, wherein the composition has a storage modulus  $G'$  of at least about 100 Pa.

22. (Original) The method of claim 21, wherein the composition has a storage modulus  $G'$  of at least about 400 Pa.

23-48. (Canceled)

**EVIDENCE - APPENDIX B**

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the Examiner is being submitted.

**RELATED PROCEEDINGS - APPENDIX C**

No related proceedings are referenced in II. above, hence copies of decisions in related proceedings are not provided.